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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/296,264	04/22/1999	JIM A. WRIGHT	032396-043	8152

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/296,264	WRIGHT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *2,3,14-16,20-22,26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,17-19,23-25,30,31,33-41,43,45-50,52-58,60* is/are rejected.

7)☒ Claim(s) *32,42,44,51,59,61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-15-04.

Claims 1-61 are pending in the instant application.

Election/Restrictions

This application contains claims 2, 3, 14-16, 20-22, 26 and 29, and SEQ ID NOS: 4, 7, 13-30, drawn to an invention nonelected with traverse in the replies filed on 10-8-02 and 4-15-04. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections and Rejections Necessitated by Amendment

Claims 6-13, 23-25, 30, 45, 46-50, 52-58 and 60 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office action mailed January 15, 2003 and August 26, 2003.

Applicant's arguments filed 4-15-04 have been fully considered but they are not persuasive. Applicants argue that one skilled in the art could make or use the invention from the disclosures in the patent and information known in the art without undue experimentation. Applicants are enabled for a method of inhibiting human tumor growth

in vivo (and inhibiting tumor cell growth in vitro) comprising the systemic administration of the antisense oligonucleotides of SEQ ID Nos: 1-3, 5, 6, 8-12 (e.g. of 20 nucleobase lengths), and of antisense oligonucleotides of this size range that specifically target and inhibit human neuropilin of SEQ ID NO: 33. Applicants are not enabled, however, for a method of inhibiting human tumor growth comprising the administration of antisense oligonucleotides of larger size range (e.g. 50-100 nucleobases). The ability to target and inhibit the target neuropilin gene using antisense in the size range of 20 nucleobases is not representative of the ability to use larger antisense (e.g. of 100 nucleobases in length). Adequate cellular delivery and uptake issues arise with larger antisense oligonucleotides, and optimal modes of delivery and cellular uptake using larger antisense would require undue experimentation beyond that provided in the instant disclosure, whereby the target gene is inhibited and tumor cell growth is inhibited.

Applicants are not enabled for a method of inhibiting the metastasis of human tumors in vivo comprising the administration of antisense oligonucleotides in vivo. The instant disclosure teaches an inhibition of metastasis of tumor cells that had been transfected in vitro with the antisense oligonucleotide of SEQ ID NO: 2 prior to administration of tumor cells in vivo. Tumor cells that had been previously transfected in vitro with antisense oligonucleotides are not considered to be representative or correlative of antisense oligonucleotide delivery in vivo and further whereby metastasis is inhibited. Likewise, inhibition of colony formation in vitro is not representative of inhibition of metastasis in vivo. Enablement for metastatic inhibition comprising the

administration of antisense oligonucleotides in vivo would require undue experimentation beyond that provided in the instant disclosure: Adequate concentrations and the appropriate cellular delivery (i.e. in concentrations required to achieve inhibition of metastasis) of antisense oligonucleotides to potentially metastatic target cells must be addressed using in vivo conditions. The conditions used to deliver adequate concentrations of inhibitory antisense oligonucleotides to tumor cells in vitro, and subsequently inject, previously transfected tumor cells into an animal, are not necessarily correlative with the in vivo delivery of antisense whereby metastasis is inhibited in that organism.

Applicant's arguments with respect to the rejection under 35 USC § 103 of claims 1, 4, 5, 31, 33-41 and 43 filed 4-15-04 have been fully considered but they are not fully persuasive. A new rejection is set forth below and the arguments that address the issues that remain relevant to the new rejection are addressed below.

Applicants argue that the prior art does not suggest or motivate one to combine the teachings of He, Milner and Baracchini. Applicants assert that nothing in the teachings of He to link the target gene encoding neuropilin with either VEGF or tumor formation. The claimed invention is drawn to compositions comprising antisense oligonucleotides (including vectors that contain antisense sequences) that specifically target and inhibit the expression of SEQ ID NO: 33 encoding human neuropilin in vitro, which antisense are nuclease resistant and are in pharmaceutical compositions, and which antisense optionally comprise one or more phosphorothioate internucleotide linkages, a morpholino backbone structure, a peptide nucleic acid, a modified base (e.g.

hypoxanthine), alkyl or heterocyclic intersugar linkages, a 2'-O-substituted ribonucleotide. Contrary to Applicants' assertions, He teaches the nucleotide sequence of the target neuropilin gene and its role in neurite outgrowth and organogenesis, thereby teaching the motivation to study the involvement of neuropilin in these biological processes. Milner teaches the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). The teachings of He, combined with the routine use of antisense oligonucleotides for inhibiting target gene expression, render the instant invention obvious to one of ordinary skill in the art of molecular biology (see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence." In addition, the examples 4 and 5, col. 17-18 of Baracchini teach the use of cellular assays for the routine determination of antisense inhibitory activity, render the instant invention obvious. This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). There is no requirement to link the different and distinct target genes VEGF and neuropilin in order to provide a proper motivation for designing and assessing antisense to study the role of neuropilin in the biological processes in cells including organogenesis and neurite

outgrowth. The routine screening techniques taught by both Milner and Baracchini apply to utilizing antisense to inhibit any target gene of known nucleotide sequence. There is no particular need to link tumor growth to neuropilin (although a lack of proper regulation of organogenesis can result in tumor formation), since the obviousness rejection addresses antisense compositions, not methods of inhibiting tumor growth.

Applicants argue that no reasonable expectation of success exists with regard to antisense and their ability to target and inhibit the expression of neuropilin. Contrary to Applicants' assertions, the combinatorial technique taught by Milner, and the previously disclosed nucleotide sequence of neuropilin (by He), allow for a simultaneous assessment of all possible oligonucleotides within a given region to inhibit target nucleic acid expression. The lack of correlation of predicted secondary mRNA structure with successful antisense inhibition was brought to light by the teachings of Milner, but this lack of correlation does not make the routine screening method for finding effective inhibitory antisense any less routine, it simply warns that one cannot design antisense based simply on secondary structural predictions. The quantity of data existing in the scientific literature (e.g. see Baracchini) showing antisense inhibition to various target genes well illustrates that a reasonable expectation of success exists in finding antisense to target and inhibit a target gene of known sequence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 5, 31, 33-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al in view of Milner et al and Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotides (including vectors that contain antisense sequences) that specifically target and inhibit the expression of SEQ ID NO: 33 encoding human neuropilin in vitro, which antisense are nuclease resistant and are in pharmaceutical compositions, and which antisense optionally comprise one or more phosphorothioate internucleotide linkages, a morpholino backbone structure, a peptide nucleic acid, a modified base (e.g. hypoxanthine), alkyl or heterocyclic intersugar linkages, a 2'-O-substituted ribonucleotide.

The references cited in this rejection were provided in the Office action mailed 8-26-03.

He et al teach the nucleotide sequence encoding SEQ ID NO: 33, human neuropilin (See entire document, especially first full paragraph on right on page 740; figure 3 on page 743; second full paragraph on left on page 748; and accession # AF018956). He et al also teach the inhibition of neuropilin to repel sensory axons using anti-neuropilin antibodies, implicating neuropilin as a receptor in neurite outgrowth (e.g. in inducing collapse of growth cones) (pages 739-740; page 744, first full paragraph; figure 4 on page 744; figure 7 on page 747). He also teaches a role of neuropilin in nonneuronal developmental processes including organogenesis, including by correlating morphological abnormalities in nonneural tissues following ectopic expession of neuropilin in transgenic mice (pages 739-740; page 744, last full paragraph).

The primary reference of He et al does not teach antisense oligonucleotides that target and inhibit the expression of SEQ ID NO: 33 encoding neuropilin in vitro, nor pharmaceutical compositions comprising these antisense, nor the incorporation of phosphorothioate internucleotide linkages, morpholoino backbone structures, peptide nucleic acids, modified bases, alkyl or heterocyclic intersugar linkates, or 2'-O-substituted ribonucleotides in antisense.

Milner et al teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence (See especially figures 5-7 on pages 539-540). This combinatorial technique taught by Milner allows for a simultaneous assessment - by

routine empirical screening methods - of all possible oligonucleotides within a given region to inhibit target gene expression (e.g. see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence.").

Baracchini et al teach the administration of pharmaceutical compositions comprising antisense oligonucleotides to appropriate cells in vitro to inhibit target gene expression and target cell growth (e.g. see examples 4 and 5, col. 17-18 of Baracchini for the use of cellular assays for the routine determination of antisense inhibitory activity). Baracchini et al teach the incorporation of one or more phorphorothioate internucleotide linkages, a morpholoino backbone structure, a peptide nucleic acid, a modified base (e.g. hypoxanthine), alkyl or heterocyclic intersugar linkages, 2'-O-substituted ribonucleotides into antisense oligonucleotides to render the antisense nuclease resistant (See col. 6, line 35-col. 8, line 62; col.17 and 18).

One of ordinary skill in the art would have been motivated to inhibit the expression of neuropilin in vitro because He teaches the role of neuropilin in neurite outgrowth in vitro by generating changes in neurite outgrowth following inhibition of neuropilin receptor activity using antibodies. He also teaches the motivation to study neuropilin expression in developmental processes by teaching the generation of morphological abnormalities associated with the ectopic expression of neuropilin. One

of ordinary skill in the art would have been motivated to design and assess antisense oligonucleotides for their ability to inhibit the expression of neuropilin in vitro because He teaches the involvement of neuropilin in the molecular mechanisms such as axon repulsion in axonal development using inhibitory antibodies (see first paragraph on page 740), and one would have been motivated to study the participation of neuropilin in these biological processes by inhibiting its expression.

One of ordinary skill in the art would have been motivated to generate antisense oligonucleotides to inhibit neuropilin expression because He teaches the nucleotide sequence encoding neuropilin, and a routine and well known way of studying the role of a molecule in a biological process in vitro is to compare the cellular process in the absence and the presence of the molecule by inhibiting its expression. Furthermore, inhibiting expression of a target molecule in vitro is routinely performed using antisense oligoncucleotides. It would have been obvious to one of ordinary skill in the art to inhibit the expression of SEQ ID NO: 33 using antisense oligonucleotides in vitro because the nucleotide sequence of human neurilin had been taught previously by He et al and the methods for inhibiting a target gene of known sequence using antisense had been taught previously by Milner et al. One of ordinary skill in the art would have expected that antisense between 15 and 50 nucleobases that are targeted to SEQ ID NO: 33 would inhibit ncuropilin expression in vitro since the routine inhibition of target gene expression using antisense in vitro was shown previously my many in the field, including Milner and Baracchini (for target genes of known nucleotide sequence). It would have been obvious to one of ordinary skill in the art to incorporate the various nuclease

resistant modifications into the antisense oligonucleotides, including phorphorothioate internucleotide modifications, morpholino backbone structures, alkyl or heterocyclic intersugar linkages, 2'-O-ribonucleotides and modified bases such as hypoxanthine into the antisense oligonucleotides because Baracchini taught the incorporation of such modifications into oligonucleotides and one of ordinary skill in the art would expect such modifications to enhance antisense stability and target binding, as taught by Baracchini et al. Milner et al additionally have taught methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have been motivated to inhibit the expression of human neuropilin of SEQ ID NO: 33 because neurilin plays a role in various cellular and developmental processes, including neurite outgrowth and organogenesis, as taught previously by He et al. Inhibiting the expression of neuropilin in cells in vitro using antisense would provide a means to compare the cellular process of neurite outgrowth (axonal repulsion) in the absence and presence of neuropilin, thereby providing insight into how the process of neurite outgrowth is affected by the participation of this target gene. It would have been obvious to administer a vector encoding antisense targeting human neuropilin to inhibit the target gene's expression in an appropriate target cell in vitro because incorporation of a nucleotide sequence into an appropriate vector for expression in a target cell is routine in the art and one would expect that an appropriate vector would allow for expression of the antisense sequence within the target cell, leading to target gene inhibition in vitro. One of ordinary skill in the art would have expected that the methods

of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al and Baracchini et al, would successfully be used for the in vitro inhibition of neurilin expression, because in vitro methods of screening a known target gene for antisense inhibition is routine in the art. The disclosure of He et al, combined with the teachings of Milner and Baracchini in disclosing the routine empirical screening of antisense for their ability to inhibit expression of any RNA target, render the instant invention obvious

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Allowable Subject Matter

SEQ ID NOS: 1-3, 5, 6, 8-12 are free of the prior art searched and of record. Claims 32, 42, 44, 51, 59 and 61 are objected to because they include additional, non-elected sequences (SEQ ID NOS: 4, 7, 13-30).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
7-27-04

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